REMARKS

Status of Claims

Claims 1-3 and 7-8 were pending. Upon entry of this Amendment, Claims 1-3 and 7-24 will be pending. Claim 1 is currently amended, and Claims 9-24 are newly added. Support for this claim amendment and for the newly introduced claims is found throughout the specification as filed. Accordingly, no new matter is introduced by way of these amendments.

Claim Rejections

Claim Rejections Under 35 U.S.C. §112, Written Description and Enablement

In the pending final Office Action, the Examiner maintained the rejection of Claims 1-3 and 7-8 as allegedly failing to comply with the written description requirement. The Examiner argued that the claim language reciting that the "composition comprises an antisense oligonucleotide of SEQ ID NO: 1" embraces any variants or fragments of antisense oligonucleotides having SEQ ID NO: 1 and reads broadly on different species of antisense oligonucleotides having SEQ ID NO: 1.

In the same Office Action, the Examiner also maintained the rejection of Claims 1-3 and 7-8 as allegedly failing to comply with the enablement requirement. The Examiner again argued that the claim language reciting that the "composition comprises an antisense oligonucleotide of SEQ ID NO: 1" embraces any variants or fragments of antisense oligonucleotides having SEQ ID NO: 1 and reads broadly on different species of antisense oligonucleotides having SEQ ID NO: 1.

Without acquiescing in the rejection, Applicants have amended claim 1 to recite that the composition "comprises the antisense oligonucleotide of SEQ ID NO: 1" as suggested by the Examiner. Support for the amendment is also found throughout the application as filed; exemplary support can be found, for example, in Paragraphs [0054], [0055], [0089], and Example 17 of the specification as published. Applicants respectfully submit that Claims 1-3 and 7-8 as amended are in compliance with the written description and enablement requirement and request withdrawal of the rejections.

Applicants note that in the Advisory Action the Examiner stated that Applicants' reply has overcome the 35 U.S.C. § 112, first paragraph, written description and enablement rejections

applied to Claims 1-3 and 7-8. However, because the Advisory Action states that Applicants' after final amendments were not entered, Applicants respectfully request that the Examiner enter the amendments submitted herewith, and withdraw the rejection of claims 1-3 and 7-8 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the enablement and written description requirements.

Double Patenting Rejection over U.S. Patent 6,169,079

Claims 1-3 were rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable in view of Claims 2-3 of U.S. Patent No. 6,169,079 ("the '079 patent"). In the final Office Action the Examiner maintains the assertion that the claims are patentably indistinct from the reference claims of the '079 patent because "the scope of claims 2-3 of U.S. Patent No. 6,169,079 B1 embraces the patent protection sought by the scope of the instant claims." *Office Action* dated 9/22/2006 at 9. Applicants respectfully traverse.

The Examiner's rationale is improper. Whether or not the scope of Claims 1-3 of the instant application are dominated by the scope of Claims 2-3 of the '079 patent is not dispositive. M.P.E.P. §804 II states:

> Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. *In re Kaplan*, 789 F.2d 1574, 1577-78, 229 USPQ 678, 681 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964). *M.P.E.P. §804 II* (emphasis added).

The Examiner has merely stated that Claims 1-3 of the instant application are dominated by Claims 2-3 of the '079 patent. The M.P.E.P. and cited case law clearly state that this is not sufficient.

Instead, the first analysis in determining whether a non-statutory basis exists for a double patenting rejection is whether any claim in the application defines an invention that is merely an obvious variation of an invention claimed in the patent. Therefore, "the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991)."

M.P.E.P.§804 II.B.1. Because the analysis parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis.

The Examiner has failed to conduct any such analysis of the *Graham* factors or establish a prima facie case of obviousness. The M.P.E.P. describes the minimum required of an Examiner asserting a claim of obviousness-type double patenting:

> Any obviousness-type double patenting rejection should make clear:
> (A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and
> (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the patent. *M.P.E.P. §804 II.B.1.*

As noted above, domination by itself is not a sufficient reason for the rejection. Thus, in the instant case the burden remains on the Examiner to establish a basis for the pending rejection.

In the present situation, the '079 patent claims a "method of inhibiting the synthesis of human intercellular adhesion molecule-1 in a cell or tissue" or "a method of treating a human having a disease with an inflammatory component which is modulated by changes in human intercellular adhesion molecule-1". The methods comprise contacting the cell or tissue (reference Claim 2) or a human (reference Claim 3) with *any* antisense oligonucleotide targeted to "a transcription initiation site, a translation initiation site, a 5'-untranslated sequence, a coding region or a 3'-untranslated sequence of an mRNA encoding human intercellular adhesion molecule-1". Accordingly, Claims 2-3 cover the use of an infinite number of antisense molecules to generically "inhibit synthesis" of ICAM-1, or to generically treat "a human having a disease with an inflammatory component".

In contrast to the generic claims, the instant claims are directed to a method of treating a species of disease, pouchitis, with a composition that includes an antisense oligonucleotide having the sequence of SEQ ID NO: 1. The instant claims are not obvious variants of generic Claims 2-3 from the '079 patent because they recite a particular use, treatment of pouchitis, using a particular compound, SEQ ID NO: 1. The Examiner provides no evidence of why the species

claimed in the instant application would be obvious in view of the generic claims from the '079 patent.

In response to Applicants' arguments submitted July 18, 2007, and repeated above, the Examiner argued in the Advisory Action that:

> Applicant's attention is directed to the fact that the instantly claimed SEQ ID NO:1 is located in the 3'-UTR of the ICAM-1. The **specification** of US 6,169,079 B1 expressly teaches that a perferred [*sic*] antisense oligonucleotide is specifically hybridized with a sequence in the 3'-UTR. See column 10. It also teaches that "The oligonucleotides used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis." See column 10. It further discloses a full-length ICAM mRNA sequence in Figure 1, and teaches that "any of the similar oligonucleotides which persons of ordinary skill in the art can prepare from knowledge of the preferred antisense targets for the modulation of the synthesis of inflammatory cell adhesion molecules." See column 12. The **specification** of US 6,169,079 B1 discloses that the antisense pharmaceutical composition can be administered in a number of ways including rectal administration and can be formulated for suppositories. See column 9. Accordingly, the generic scope of the claimed method in the reference claims of US 6,169,079 B1 embraces the narrow scope of the instantly claimed invention and since the US patent expressly teaches that anyone of ordinary skill in the art can locate a preferred [*sic*] antisense target for modulation of inflammatory cell adhesion molecules given that the target ICAM-1 mRNA sequence is provided, the instantly claimed invention is an obvious variation of the generic, broad claims in the US patent. Accordingly, claims 1-3 as well as claims 7-8 (by claim dependency) remain rejected. *Advisory Action* at 2 (emphasis added).

The Examiner's entire argument is impermissibly based on the teachings of the specification of the '079 patent. The M.P.E.P. and caselaw are unambiguous in stating that the specification of cited patent may not be considered in making an obviousness-type double patenting rejection because the cited patent is not available as prior art under any statute (*e.g.*, the cited patent is not prior art under 35 U.S.C. §§ 102 or 103):

> When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). This does not mean that one is precluded from all use of the patent disclosure. *M.P.E.P. §804 II.B.1* (emphasis added).

The disclosure of the cited patent can be considered for only two limited reasons. The first is to learn the meaning of a term in the patent claim, in which case the specification is used as a dictionary. *See Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). The second is to determine what is claimed by looking to an embodiment of the invention disclosed in the specification. This is done to assist the Examiner in determining what is claimed. *See In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970).

Neither of these exceptions apply to the instant case. The Examiner's response in the Advisory Action is not using the specification of the '079 patent to define a claim term or to better understand the scope of the claims. Instead, the Examiner is relying on the teachings of the '079 patent as a prior art reference to provide a basis for one of skill in the art to select the species of pouchitis and SEQ ID NO:1. This is impermissible, as Claims 1-3 of the instant application must be obvious over the claims of the '079 patent, not the entire disclosure of the '079 patent. Were the Examiner permitted to apply the entire disclosure of the '079 patent as prior art, it would eviscerate the statutory definition of prior art found in 35 U.S.C. §§ 102 and 103 – the Examiner would be applying a reference as prior art which is not prior art under any statute.

In sum, mere domination of claims 1-3 by the claims of the '079 patent is not a sufficient basis for an obviousness-type double patenting rejection. It is the Examiner's responsibility to provide a reasoned basis for stating that the claimed subject matter is obvious over the claims of the '079 patent, without impermissibly relying on the disclosure of the '079 patent. Because the Examiner has not provided any permissible basis for considering the selection of the species pouchitis and SEQ ID NO:1 obvious over the claims of the '079 patent, the obviousness-type rejection of Claims 1-3 must be withdrawn.

Double Patenting Rejections over U.S. Patent 5,591,623

The Examiner also rejects Claim 1 on the ground of non-statutory obviousness-type double patenting as being unpatentable over Claims 2 and 4 of U.S. Patent No. 5,591,623 ("the '623 patent") in view of Patel et al. (1995, *European Journal of Gastroenterology & Hepatology* 7:1037-1041). To support the rejection, the Examiner makes the following argument:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed SEQ ID NO: 1 is identical to SEQ ID NO:22 claimed in the reference claims of 5,591,623. Although the reference claims do not expressly recite a "method of treating pouchitis in a human in need thereof", the methods claimed in the reference claims embrace the instantly claimed invention because the specification of 5,591,623 discloses that "an animal suspected of having a disease which can be treated by decreasing the expression of ICAM-I" is "treated by administering oligonucleotides in accordance with this invention". See column 7, lines 25-28. Patel et al. teach that patients with pouchitis have significantly high level of plasma ICAM-1. ... Since the correlation between the high plasma level of ICAM-1 and pouchitis has been shown by Patel et al. it would have been obvious to practice the claimed invention in U.S. Patent No. 5,591,623 for treating pouchitis as claimed in the instant case. The skilled artisan would have been motivated to do so with a reasonable expectation of success because the specification of 5,591,623 expressly discloses that the method of using SEQ ID NO:22 (ICAM-1 antisense oligonucleotide that is ISIS 2302) can be used to treat ICAM-1 associated disease in an animal. *Office Action* at 7 (emphasis added).

As discussed above, the M.P.E.P. and caselaw clearly state that the disclosure of a cited patent cannot be used as the basis for the obviousness-type double patenting rejection:

> When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). *M.P.E.P. §804 II.B.1* (emphasis added).

As discussed above, the disclosure of the cited patent can only be used to define a claim term or to assist the Examiner in determining the scope of the referenced claim. This is not what the Examiner has done in the instant case.

Instead, the Examiner is impermissibly using the disclosure of the '623 patent as a basis for establishing two of the elements of a prima facie case of obviousness. The Examiner cites the statement in the specification of the '623 patent that antisense to ICAM-1 can be used to treat disease in animals as the basis for the motivation and likelihood of success prongs of a prima facie case of obviousness. The Examiner's arguments are impermissibly using the disclosure of the '623 as prior art when only the claims of the '623 patent are available to the Examiner.

As Applicants have previously argued, the reference claims of the '623 patent recite a "method of inhibiting synthesis of intercellular adhesion molecules in a cell comprising contacting the cell in vitro" with "an oligonucleotide having SEQ ID NO: 22" (Claim 2) or with

"an oligonucleotide having SEQ ID NO: 1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 17, 20, 21, 23, 24, 25, 26 or 27" (Claim 4). The cited claims of the '623 patent relate to methods of inhibiting synthesis of intercellular adhesion molecules in a cell ***in vitro***. In contrast, instant Claim 1 is directed towards an ***in vivo*** method of treating a specific disease, pouchitis in a human, with a pharmaceutical composition that comprises the antisense oligonucleotide of SEQ ID NO: 1. The instant claims recite a new use, the *in vivo* treatment of pouchitis in a human, as well as a distinct element, the pharmaceutical composition.

Although Patel discloses a correlation between high plasma level of ICAM-1 and pouchitis, there is no teaching in Patel that decreasing ICAM-1 levels would treat pouchitis. Patel suggests the use of ICAM-1 as a *marker* of continuing inflammation, but does not provide a basis for concluding that inhibiting this marker would provide a therapeutic benefit for pouchitis.

In response to Applicants' arguments, the Examiner makes the following argument:

> Since Patel et al. taught patients with pouchitis have high level of ICAM-1 expression, and since the antisense compound claimed in the reference claims was known to inhibit ICAM-1 expression in cells, it would have been obvious to one of ordinary skill in the art to use the antisense compound of the reference claims for treating patients with pouchitis by reducing the level of ICAM-1 expression via the ICAM-1 specific antisense compound of US Patent 5,591,623. One of ordinary skill in the art would have been motivated to make and use a method of treating pouchitis in a patient comprising administering the anti-ICAM-1 antisense compound of US Patent 5,591,623, with a reasonable expectation of success, because antisense compounds were known to be applicable for in vivo therapeutic use at the time the invention was made and because inhibiting ICAM-1 expression level was known to "provide a new target for the control of inflammatory bowel disease" including pouchitis. See the last sentence on page 1040 of Patel et al. Accordingly, the instantly claimed invention would have been prima facie obvious over claimed reference methods in view of the teachings of Patel et al. *Advisory Action* at 2 (emphasis added).

The Examiner's argument fails for at least two reasons. First, it ignores the fact that Patel's statement does not specifically mention inhibiting ICAM-1 expression as a therapy for pouchitis, or provide any basis for believing such a treatment would be successful. Instead, Patel states that "[i]nhibition of these leucocyte-endothelial cell interactions might cause decreased leucocyte transmigration to the site of inflammation and could, hypothetically, provide a new target for control of inflammatory bowel disease." *Patel* at 1040, last sentence (emphasis added). This statement by Patel provides no reasonable expectation of success for treating pouchitis using

antisense to ICAM-1. It is merely an invitation to investigate a possible, hypothetical, target for treatment. Accordingly, Patel does not provide a reasonable expectation of success for treating pouchitis with the antisense molecules of the claimed methods. states that targeting ICAM-1

Second, Applicants note that the Examiner's statements that antisense data "in cells" are sufficient to provide a reasonable expectation of success for "treating patients," and that "antisense compounds were known to be applicable for in vivo therapeutic use at the time the invention was made," are in direct conflict with the Examiner's previous statements. The Examiner previously argued that:

> [O]ne of ordinary skill in the art would not be able to predict the therapeutic outcomes of oligonucleotides targeted to ICAM-l mRNA sequence in the absence of clinical data. The unpredictable pharmacokinetics of DNA-based drugs as taught by Patil et al. thus would necessitate undue experimentation for one skilled in the art to ascertain the "pharmacological outcomes" of the claimed oligonucleotide targeted to ICAM-l mRNA for the treatment of pouchitis in a human patient.
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> ***
>
> Given the unpredictable nature of DNA-based drugs in vivo and the lack of specific guidance to practice the method of treating pouchitis in human patients by administering any other pharmaceutical compositions than the instantly tested ISIS-2302, one of ordinary skill cannot practice the instant invention without undue experimentation... Again, due to the unpredictable nature of DNA-based drugs as taught by Patil et al., one skilled in the art cannot extrapolate the improved pharmacological effects of the ICAM-I oligonucleotide compositions merely based on healthy rat model studies.
>
> ...One skilled in the art cannot predict that the claimed method of treating pouchitis in a human patient will be effective, if other than ISIS-2302 compound ...was administered to the patient, particularly since the specification has not set forth any other compositions that are capable of treating pouchitis required by claims 1-8. It is well known that the art of nucleic acid- based drug discovery for therapy is highly unpredictable as stated above. It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method drawn to treating pouchitis would be used without undue experimentation. *Office Action dated 9/22/2006* at 6-7 (emphasis added).

These statements by the Examiner make it clear that it is the Examiner's position that the *in vivo* use of antisense compositions is highly unpredictable, even in the face of *in vivo* animal studies. The Examiner has concluded that "based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method drawn

to treating pouchitis would be used without undue experimentation." *Id.* at 7. Neither the '623 patent nor Patel provide any experimental evidence of *in vivo* treatment of pouchitis using ICAM-1 antisense. Applicants submit that it is inconsistent for the Examiner to now argue that the instant claims to a method of treating pouchitis *in vivo* are prima facie obvious. It is the Examiner's stated position that the use of antisense for *in vivo* therapy is highly unpredictable and requires experimental evidence before it will be accepted by those of skill in the art. Based on the Examiner's previously stated positions, the Examiner must conclude that there is no reasonable expectation of success based on the claims of the '623 patent and Patel.

In view of the foregoing remarks, Applicants submit that the method of treating pouchitis *in vivo* of the instant application is not an obvious variant of the *in vitro* methods recited in Claims 2 and 4 of the '623 patent. Applicants therefore respectfully request the withdrawal of the obviousness-type double-patenting rejection of Claim 1.

Conclusion

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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